REMARKS

Status of the Claims

Claims 1, 11-16, 19-27, 32-35, 44, and 45 are currently pending and under examination. Applicants have canceled claims 36-40 and 43 without prejudice or disclaimer of the subject matter of those claims. Claim 35 is amended to correct a grammatical error. Applicants have also amended claim 26 to remove a hyphen from the term "butylthiophene." Applicants have amended claim 1 to indicate that "Z_2 represents -CH- or -N-." Applicants have also added new claim 44, which recites Applicants' elected species. New claim 45 recites a pharmaceutically-acceptable salt of of Applicants' elected species. Support for the amendment to claim 1 and for new claims 44 and 45 can be found throughout the specification at, for example, pages 4 and 5, Example 1, and in the original claims. Applicants contend that neither the claim amendments nor claims 44 and 45 add new matter.

Applicants acknowledge with appreciation the Examiner's withdrawal of the prior rejection of claim 26 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Claims 1, 11-16, 19-27, and 32-35 remain rejected under 35 U.S.C. § 103(a). Applicants address this single remaining rejection below.

Interview

Applicants wish to thank the Examiner for the interview held on February 24, 2009, with Applicants' representatives. At the interview, the attached declaration was discussed along with withdrawn claims 36 and 43. The substance of this discussion is contained in the remarks below. Applicants note that the attached declaration contains four minor changes, in comparison to the declaration discussed on

February 24, 2009, for clarification purposes. These changes are located in paragraphs 14, 16, 21, and 27 of the attached declaration.

Specification

The Examiner noted that the filing date of application PCT/GB02/02563 appears to be incorrectly indicated at page 1 of the specification. Office Action, page 3. Applicants amended the filing date of PCT/GB02/02563 on page 1, lines 5-6 of the instant specification to reflect an international filing date of May 30, 2002. Applicants therefore request that the Examiner withdraw this objection to the specification.

Rejection Under 35 U.S.C. § 103

Claims 1, 11-16, 19-27 and 32-35 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over EP 0 512 675 ("Allen"). According to the Examiner, Allen teaches "imidazole compounds that are structurally similar to the instant claimed compounds and are useful in treating . . . hypertension," particularly referring to Compound 51 on page 65. Office Action, pages 4-5. Acknowledging that Allen does not teach a hydrogen at the 2-position of the imidazole ring, the Examiner contends that Allen does teach a lower alkyl at that position. *Id.* at 5.

Based on the alleged teachings of Allen, the Examiner concludes that "the substitution of a hydrogen atom for a lower alkyl on a known compound is not a patentabale modification *absent unexpected or unobvious results*." Office Action, pages 5-6; emphasis added. According to the Examiner,

> ...those skilled in [the] chemical art [would appreciate that] one homologue is not such an advance over [an] adjacent member of [a] series as requires invention because chemists knowing properties of one member of [the] series would in general know what to expect in adjacent members.

> . . . The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (*i.e., an angiotension II antagonist*).

Office Action, page 6; emphasis added.

Applicants respectfully disagree with the "expectation" that structurally similar compounds would possess similar activity, upon which the Examiner bases an alleged motivation to make the claimed compounds. If anything, those in the art understood that a change in a compound's chemical structure could result in a significant change in the compound's properties. In this case, contrary to the Examiner's assumption that the claimed compounds would have angiotensin II ("AngII") antagonist activity, the claimed compounds in fact have AngII agonist activity. Indeed, the claimed compounds have both different properties from Allen's compounds and, as the attached declaration explains, a different utility, clearly demonstrating the "unexpected and unobvious results" that make the claimed compounds patentable.

A. A Change in Chemical Structure Can Produce a Significant Change in Properties

As Applicants noted above, those of ordinary skill in the art understood that a change in a compound's chemical structure could result in a significant change in the compound's properties. At the time of the invention, artisans knew that the "intrinsic activity [of a drug is] determined by its chemical structure." E. M. Ross. Pharmacodynamics: *Mechanisms of drug action and the relationship between drug concentration and effect* in: J. G. Hardman *et al* (eds.): *Goodman & Gilman's - The Pharmacological Basis of Therapeutics*, 9th Ed., McGraw-Hill, New York, 1996, at page 30, left column (Exhibit E of the attached declaration; "Ross"). The Court of Appeals for

the Federal Circuit also recognizes this principle. *See Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (The patentability of a chemical compound does not depend only on structural similarity.) and *In re Papesch*, 315 F.2d 381 (CCPA 1963) (A compound and its properties are inseparable.). As Ross also instructs, "[r]elatively minor modifications in the drug molecule may result in major changes in pharmacological properties." *Id.* Indeed, two drugs that bind to the same receptor at the same site can have opposite properties, one drug being an agonist, the other an antagonist. *See Id.* at 39, right column. Thus, contrary to the Examiner's description of what artisans expected of allegedly similar compounds, this "expectation" was far from certain.

Indeed, the skilled artisan appreciated the extreme difficulties in the pharmacological art associated with creating small molecules that have agonist activity at any receptor as well as the level of unpredictability associated with such small molecules. In fact, the claimed compounds are believed to be the first small molecule (i.e. non-peptide) AT2 receptor-specific agonists ever described. *See* paragraph 4 of Declaration. Thus, the newly-discovered pharmacological effect provided by the present invention provides the public with a completely new invention, which could in no way have been derived from the cited prior art by one of ordinary skill, much less have been predicted to have agonist activity. As the MPEP instructs, "[i]f the technology is unpredictable, it is less likely that structurally similar species will render a claimed species obvious because it may not be reasonable to infer that they would share similar properties." MPEP § 2144.08(II)(A)(4)(e).

In sum, the Examiner's underlying assumption as to why one of ordinary skill in the art would have been motivated to make the substitution at the 2-position of the imidazole ring suggested by the Examiner is incorrect. If anything, artisans knew that changes to a chemical structure could result in significant changes to the properties and utility of a compound. Applicants discuss these differences in properties and utility below. Given that the Examiner has not provided a basis for motivation, Applicants contend that the Examiner has not established a *prima facie* case of obviousness. On this ground alone, Applicants believe that this rejection should be withdrawn.

B. The Properties of the Claimed Compounds Are Completely Different from the Properties of Allen's Compounds

Arguendo, if the Examiner's assumption that structurally similar compounds would have similar properties were correct and if one were to agree that the claimed compounds were structurally similar to Allen's compounds, then the fact that Allen's compounds and the claimed compounds have completely different properties clearly constitutes "unexpected" and "unobvious" results.

Allen teaches that their compounds are AngII antagonists, while the compounds of the present invention are AngII agonists. As emphasized in the cases cited above, this distinction is part of the obviousness analysis that must be considered by the Examiner when she considers the invention as a whole. In fact, this unexpected difference, alone, patentably distinguishes the presently claimed compounds from those of the cited prior art because the activity of the compounds disclosed by Allen is entirely different from the presently claimed compounds. To further elaborate on this point, Applicants attach a declaration by Dr. Thomas Unger, an expert in pharmacology and

the condition of hypertension. As explained in Dr. Unger's declaration ("Declaration"), drugs that bind to physiological receptors and mimic the effect of the natural, endogenous ligand are termed agonists, whereas those that bind to receptors and do not mimic, but interfere with the binding of the endogenous ligand are termed antagonists. *See* paragraph 12 of Declaration. Antagonists are themselves devoid of any intrinsic (receptor stimulating) activity, but they produce effects by inhibiting the action of the natural ligand by competition for the ligand binding sites. *Id.*

Based on the screening assays disclosed in Allen, Applicants believe that the compounds disclosed in Allen are AngII AT1 receptor antagonists. *See* paragraph 8 of Declaration. The compounds of Allen present quite different biological activity compared to the activity exhibited by the presently claimed compounds. *Id.* Specifically, the compounds presently claimed are agonists of the angiotensin II type 2 (the AT2) sub-receptor. In particular, they are agonists that bind selectively to the AT2 subtype receptor. As Example 14 of the instant specification demonstrates, the compounds of the examples bind to the AT2 receptor as shown by an affinity for AT2 receptors of less than Ki = 100 nM and an affinity for the other angiotensin II receptor (AT1) of more than Ki = 500 nM. Agonism of the AT2 sub-receptor is also positively demonstrated by way of Example 15 (see paragraph 5 of the Declaration).

Moreover, Dr. Unger's declaration also presents and discusses data that directly shows the difference in properties between the compound of Example 1, the species elected by Applicants, and Allen's Compound 51. Consistent with the above statements, these data also show that the compound of Example 1 is an AngII AT2 receptor agonist while Compound 51 is mainly an AngII AT1 antagonist with possible

AT2 antagonist properties also. *See* Declaration at paragraphs 26 and 27 with Figure 1 and at paragraphs 28-31 with Figure 2. In light of these data, Dr. Unger concludes that "a structural change to the compounds of Allen . . . to arrive at the presently-claimed compounds has resulted in a completely different (i.e. a ***change*** in) biological activity." Declaration, paragraph 32, emphasis in original.

In addition, Dr. Unger explains the importance of AngII receptor specificity, noting that the presently-claimed compounds are AT2 subtype specific, whereas Allen *et al*'s Compound 51 appears to act as an antagonist mainly via AT1, but also possibly via AT2. *Id.* For compounds that affect AngII signalling, receptor subtype specificity is important so that the desired results (i.e., treating the consequences of hypertension such as inflammation) are targeted. Thus, the claimed compounds provide superior results in that (1) they are AT2 agonists that are likely to have a much broader range of activity in the clinic than AT1 receptor antagonists (*see* Declaration at paragraphs 16-22) and (2) they are specific to the AT2 sub-type receptor.

Given these clear differences between the properties of Allen's compounds and the claimed compounds, it is not suprising that there is nothing in that reference to suggest that making the modification suggested by the Examiner would lead not only to a switch from antagonism of a receptor to agonism of a receptor, but also to selective agonism of a different receptor sub-type. This, in itself, illustrates an entirely unexpected result to a person skilled in the art. *See* paragraph 9 of the Declaration.

C. *The Utility of the Claimed Compounds Is Completely Different from the Utility of Allen's Compounds*

The Examiner suggests that one of ordinary skill in the art would have been "motivated to prepare homologs of the compounds taught by Allen . . . to arrive at the instant claimed compounds [to obtain] compounds which would be useful in treating . . . hypertension." Office Action, pages 6 and 7. As Dr. Unger's declaration attests, however, the beneficial effects of the claimed agonist compounds go beyond the effects that result from using Allen's antagonist compounds.

In summary, the Dr. Unger makes clear that AT2 agonism is likely to give rise to a much broader and clinically beneficial range of activity than is available from treatment with AT1 receptor antagonists. *See* Declaration, paragraph 22. Specifically, he explains that AT2 receptor agonists are likely to have a much broader range of activity in the clinic than AT1 receptor antagonists for at least the following reasons. The AT2 receptor agonists potentially:

(a) are useful in the ***direct*** healing of organic diseases that are related to conditions such as hypertension;

(b) give rise to a much broader range of anti-inflammatory and anti-fibrotic activity than is possible with AT1 receptor antagonists; and

(c) are useful in the treatment of diseases that cannot be treated by simple blockade of the AT1 receptor. *See Id.*

Thus, one of ordinary skill in the art seeking to develop AT2 receptor agonists for treating the consequences of hypertension, such as inflammation, hypertrophy and

fibrosis would not have even looked to Allen's teaching regarding AT1 receptor antagonists, much less have been motivated to modify the disclosed AT1 receptor antagonist to arrive at the claimed AT2 receptor agonist compounds. *See* paragraph 17 and 33 of Declaration. As a result, it would not have been obvious from a fair reading of Allen, as a whole, to make the suggested structural modification to produce the claimed AT2 receptor agonist compounds given this difference in the utility between the claimed compounds and Allen's compounds. *Id.* at paragraph 33.

D. Allen Teaches Away from the Claimed Compounds

Applicants previously argued that Allen teaches away from an unsubstituted carbon at the 2-position of the imidazole ring. Specifically, Allen states that their invention is directed to substituted imidazoles, with substitution specifically at the specificed positions. *See* Amendment filed December 12, 2007, at page 14. Since the only position on the imidazole ring that is specified as having a substituent is exactly the position where the instantly claimed compounds have no substituent, Allen teaches away from modifying the compound to arrive at the claimed compounds. *Id.*

In response to this argument, the Examiner contends that the "instant specification and the originally filed claims in the instant application . . . also discloses and [claims] the equivalency of hydrogen and $C_{1\text{-}6}$ alkyl at the 2-position of an imidazole ring," referring to the definition of the R^1 variable. Office Action, pages 9 and 10. Applicanst respectfully disagree. The instant specification provides no such teaching.

Both original claim 1 and the specification at page 4, lines 20 and 21 contain a proviso that says "when X_1 represents $-C(R^1)-$, X_3 represents $-C(R^2)-$ and X_4 represents $-C(R^3)-$, then R^1 represents H." In the case of an imidazole ring, X_2 represents N, which

means that X_1 represents -C(R^1)-, X_3 represents -C(R^2)- and X_4 represents -C(R^3)-. As described by the proviso, therefore, R^1 represents H. Thus, in the case of an imidazole ring, neither the specification nor the original claims teach the equivalency of hydrogen and a C_{1-6} alkyl at the 2-position of an imidazole ring as the Examiner suggests.

Clearly, Allen teaches a substitution at the 2-position of the imidazole ring when the instant invention consistently does not. As the MPEP instructs, "[t]eachings of preferred species of a complex nature within a disclosed genus may motivate an artisan . . . to make similar complex species and thus teach away from making simple species within the genus." MPEP § 2144.08(II)(A)(4)(c). Allen's consistent teaching towards the more complex, substituted species, teaches away from the instant invention's teaching towards the more simple species.

E. Conclusion

The structural difference between the compounds of Allen and the presently claimed compounds give rise to unexpected, beneficial and superior results. *See* paragraph 32 of the Declaration. A structural change to the compounds of Allen to arrive at the presently-claimed compounds resulted in completely different properties. As a direct consequence of this change in properties, the presently claimed compounds are expected to have different utilities in the clinical setting for the reasons set out above and as explained in the accompanying declaration. Specifically, AT2 receptor agonists, such as those presently claimed, are more likely to have a direct positive and more beneficial effect on the consequences of hypertension, such as inflammation, hypertrophy and fibrosis in addition to more targeted affects due to the AT2 receptor specificity of the claimed compounds. Moreover, the Examiner's basis for motivation to

make the suggested change to Allen's compounds is not reflective of what was known in the art about the impact of changes to chemical structure on compound properties. Finally, in addition to the unexpected differences enumerated above, Allen also teaches away from the claimed compounds.

For these reasons, Applicants request withdrawal of the obviousness rejection of claims 1, 11-16, 19-27 and 32-35.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of claims 1, 11-16, 19-27, 32-35, 44, and 45.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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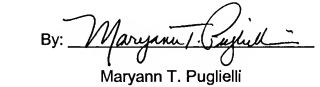
Date: March 13, 2009

By: 

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